General

Guideline Title

Diagnosis and management of chronic graft-versus-host disease.

Bibliographic Source(s)

Dignan FL, Amrolia P, Clark A, Cornish J, Jackson G, Mahendra P, Scarisbrick JJ, Taylor PC, Shaw BE, Potter MN, on behalf of the Haemato-oncology Task Force of the British Committee [trunc]. Diagnosis and management of chronic graft-versus-host disease. Br J Haematol. 2012 Jul;158(1):46-61. [125 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Note from the British Committee for Standards in Haematology (BCSH): The BCSH guidelines on graft-versus-host disease have been split into three documents, which are designed to be used together and to complement each other in order to provide an evidence-based approach to managing this complex disorder. In addition to the current document, the following national Guideline Clearinghouse (NGC) summaries are available:

Diagnosis and management of acute graft-versus-host disease
Organ-specific management and supportive care in graft-versus-host disease

Definitions for the quality of the evidence (A-C) and strength of recommendation (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

Diagnosis

- Chronic graft-versus-host disease (GvHD) and overlap syndrome should be diagnosed primarily using clinical criteria, supported by biopsy when possible (1B).

Grading

- Chronic GvHD should be graded as mild, moderate, or severe according to National Institutes of Health (NIH) consensus criteria (Filipovich et al., 2005) (1A).
- All patients with signs or symptoms suggestive of chronic GvHD in one organ should be assessed for involvement of other organs (1A).

Principles of Chronic GvHD Treatment

First Line Systemic Treatment for Chronic GvHD

- Corticosteroids are recommended in the first line treatment of chronic GvHD (1A).
- An initial starting dose of 1 mg/kg prednisolone is recommended (1B).
- Calcineurin inhibitors may be helpful in the initial treatment of GvHD as a steroid sparer (2C).

Second-Line Systemic Treatment in Chronic GvHD

- Extra-corporeal photopheresis (ECP) may be considered as a second line treatment in skin, oral, or liver chronic GvHD (1B).
- ECP schedule should be fortnightly-paired treatments for a minimum assessment period of 3 months (1C).
- Mammalian target of rapamycin (mTOR) inhibitors are suggested as a second line treatment option in refractory chronic GvHD (2C).
- Pentostatin is suggested as a second line treatment option in refractory chronic GvHD (2B).
- Rituximab is suggested as a second line treatment option in refractory cutaneous or musculoskeletal chronic GvHD (2B).
- Imatinib is suggested as a second line treatment option in refractory pulmonary or sclerodermatous chronic GvHD (2C).
- ECP, imatinib, and rituximab may be considered as third line treatment options in chronic GvHD involving other organs (2C).

Third Line Treatment Options

- The following agents are suggested as third line treatment options in refractory chronic GvHD: mycophenolate mofetil, methotrexate, pulsed corticosteroids (2C).

Other Agents

- There is insufficient evidence at present to recommend the use of the following agents in the management of chronic GvHD: cyclophosphamide, mesenchymal stem cells (MSCs), thalidomide, retinoids, alemtuzumab, infliximab, etanercept, clofazimine, alefacept, daclizumab, basiliximab, hydroxychloroquine, thoraco-abdominal irradiation (1C).
- Azathioprine is not recommended in the management of chronic GvHD due to the risk of oral malignancy (1C).

Definitions:

Quality of Evidence

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series, or just opinion.

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Clinical Algorithm(s)

The original guideline document contains a clinical algorithm for first, second, and third line treatment options in chronic graft-versus-host disease (GvHD).

Scope

Disease/Condition(s)

Chronic graft-versus-host disease (GvHD)

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Allergy and Immunology

Endocrinology

Gastroenterology

Hematology

Obstetrics and Gynecology

Oncology

Ophthalmology

Pediatrics

Rheumatology

Intended Users

Occupational Therapists

Physical Therapists

Physician Assistants

Physicians

Guideline Objective(s)

To provide an evidence-based approach to diagnosis, staging, and management of chronic graft-versus-host (GvHD) disease

Target Population

Adults and children in the United Kingdom with chronic graft-versus-host disease (GvHD) following allogeneic stem cell transplant

Interventions and Practices Considered

Diagnosis/Evaluation

1. Use of clinical criteria for diagnosis of chronic graft-versus-host disease (GvHD) or overlap disease
2. Use of biopsy when necessary to confirm diagnosis
3. Grading GvHD according to National Institutes of Health (NIH) consensus criteria

Treatment/Management

1. First line treatment with systemic corticosteroids
    - Dose of corticosteroids
    - Use of calcineurin inhibitors as a corticosteroid sparer
2. Second line treatment based on organ involvement
    - Extra-corporeal photopheresis (ECP) in skin, oral or liver GvHD
    - ECP schedule
    - Mammalian target of rapamycin (mTOR) inhibitors or pentostatin in refractory GvHD
    - Rituximab in refractory cutaneous or musculoskeletal GvHD
    - Imatinib in refractory pulmonary or sclerodermatous GvHD
    - ECP, imatinib or rituximab in GvHD involving other organs
3. Third line treatment: mycophenolate mofetil, methotrexate, pulsed corticosteroids

Note: The following treatments were considered but not recommended because of insufficient evidence: cyclophosphamide, mesenteric stem cells, thalidomide, retinoids, alemtuzumab, infliximab, etanercept, clofazimine, alefacept, daclizumab, basiliximab, hydroxychloroquine, thoraco-abdominal irradiation.

Note: The following treatment was considered but not recommended: azathioprine.

Major Outcomes Considered

- Specificity of clinical symptoms and signs of chronic graft-versus-host disease (GvHD)
- Incidence of overlapping acute and GvHD symptoms
- Incidence of need for biopsy to confirm GvHD
- Timing of appearance of symptoms
- Predictive value of prognostic factors
- Complete and partial response rates to treatment
- Side effects of treatments
- Overall and 1 to 10-year survival rates
- Non-relapse mortality
- Incidence and severity of steroid-refractory GvHD

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The production of these guidelines involved a literature review to 17th June 2011 including Medline, internet searches, and major conference reports.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series, or just opinion.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

The production of these guidelines involved the following step:

- The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The production of these guidelines involved the following steps:

- Establishment of a working group comprising experts in the field of allogeneic transplantation followed by literature review.
- Development of key recommendations based on randomized, controlled trial evidence. Due to the paucity of randomized studies some recommendations are based on literature review and a consensus of expert opinion.
- The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used assess the strength of recommendations. The GRADE criteria are specified in the British Committee for Standards in Haematology (BCSH) guideline pack and

the GRADE working group website (see the 'Rating Scheme for the Strength of Recommendations' field). Further information is available from the following websites:

- http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html
- http://www.gradeworkinggroup.org/index.htm

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Cost Analysis

A formal cost analysis was not performed and published analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The production of these guidelines involved the following steps:

- Review by the British Committee for Standards in Haematology (BCSH) committees, British Society of Blood and Marrow Transplantation (BSBMT) executive committee, the UK Photopheresis Society and the UK Paediatric Bone Marrow Transplant Group
- Review by sounding board of the British Society for Haematology (BSH) and allogeneic transplant centres in the UK

Evidence Supporting the Recommendations

References Supporting the Recommendations

Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, Martin P, Chien J, Przepiorka D, Couriel D, Cowen EW, Dinndorf P, Farrell A, Hartzman R, Henslee-Downey J, Jacobsohn D, McDonald G, Mittleman B, Rizzo JD, Robinson M, Schubert M, Schultz K, Shulman H, Turner M, Vogelsang G, Flowers ME. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005 Dec;11(12):945-56. PubMed

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis and management of chronic graft-versus-host disease (GvHD), which may lead to effective control of GvHD while minimizing the risk of toxicity and relapse

Potential Harms

- See Table 1 in the original guideline document for a summary of the major toxicities of chronic graft-versus-host disease (GvHD) treatments.
- Mammalian target of rapamycin (mTOR) should be used with caution in combination with calcineurin inhibitors in view of the risk of thrombotic microangiopathy and trough levels should be monitored. Patients should also be monitored for hyperlipidaemia. Care should be taken to avoid toxicity due to interactions with other medications, particularly azoles.
- All treatment options for third line treatment are likely to be associated with a high risk of infection.

Contraindications

Contraindications

- As infections are frequent, it has been recommended that pentostatin is not used in the context of acute infection or in pulmonary chronic graft-versus-host disease (GvHD).
- Azathioprine is not recommended in the management of GvHD due to the risk of oral malignancy.

Qualifying Statements

Qualifying Statements

- The agents that may be considered for third line treatment options (mycophenolate mofetil, methotrexate, and pulsed corticosteroids) are considered to be third line options as there is less evidence available for their use. The authors acknowledge that some of these agents have not been studied in the context of third line treatment of chronic graft-versus-host disease (GvHD).
- While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology, the British Society of Blood and Marrow Transplantation nor the publishers accept any legal responsibility for the content of these guidelines.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Jul

Guideline Developer(s)

British Society for Haematology Guidelines - Professional Association

British Society of Blood and Marrow Transplantation - Professional Association

Source(s) of Funding

British Committee for Standards in Haematology

Guideline Committee

Joint Working Group of the British Committee for Standards in Haematology (BCSH) and the British Society of Blood and Marrow Transplantation (BSBMT)

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Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the British Committee for Standards in Haematology Web site .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on July 30, 2012. The information was verified by the guideline developer on September 5, 2012. This summary was updated by ECRI Institute on November 21, 2013 following the U.S. Food and Drug Administration advisory on Arzerra (ofatumumab) and Rituxan (rituximab).

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